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Context Persons with schizophrenia are thought to be at increased risk of committing violent crime 4 to 6 times the level of general population individuals without this disorder. However, risk estimates vary substantially across studies, and considerable uncertainty exists as to what mediates this elevated risk. Despite this uncertainty, current guidelines recommend that violence risk assessment should be conducted for all patients with schizophrenia.

Objective To determine the risk of violent crime among patients diagnosed as having schizophrenia and the role of substance abuse in mediating this risk.

Design, Setting, and Participants Longitudinal designs were used to link data from nationwide Swedish registers of hospital admissions and criminal convictions in 1973-2006. Risk of violent crime in patients after diagnosis of schizophrenia (n=8003) was compared with that among general population controls (n=80 025). Potential confounders (age, sex, income, and marital and immigrant status) and mediators (substance abuse comorbidity) were measured at baseline. To study familial confounding, we also investigated risk of violence among unaffected siblings (n=8123) of patients with schizophrenia. Information on treatment was not available.

Main Outcome Measure Violent crime (any criminal conviction for homicide, assault, robbery, arson, any sexual offense, illegal threats, or intimidation).

Results In patients with schizophrenia, 1054 (13.2%) had at least 1 violent offense compared with 4276 (5.3%) of general population controls (adjusted odds ratio [OR], 2.0; 95% confidence interval [CI], 1.8-2.2). The risk was mostly confined to patients with substance abuse comorbidity (of whom 27.6% committed an offense), yielding an increased risk of violent crime among such patients (adjusted OR, 4.4; 95% CI, 3.9-5.0), whereas the risk increase was small in schizophrenia patients without substance abuse comorbidity (8.5% of whom had at least 1 violent offense; adjusted OR, 1.2; 95% CI, 1.1-1.4; $P<.001$ for interaction). The risk increase among those with substance abuse comorbidity was significantly less pronounced when unaffected siblings were used as controls (28.3% of those with schizophrenia had a violent offense compared with 17.9% of their unaffected siblings; adjusted OR, 1.8; 95% CI, 1.4-2.4; $P<.001$ for interaction), suggesting significant familial (genetic or early environmental) confounding of the association between schizophrenia and violence.

Conclusions Schizophrenia was associated with an increased risk of violent crime in this longitudinal study. This association was attenuated by adjustment for substance abuse, suggesting a mediating effect. The role of risk assessment, management, and treatment in individuals with comorbidity needs further examination.

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More than 20 epidemiological studies have reported on the association between major mental disorder and violence, including more than 10 that specifically have examined the relationship with schizophrenia.[1] These reports typically find that schizophrenia is related to a 4- to 6-fold increased risk of violent behavior, which has led to the view that schizophrenia and other major mental disorders are preventable causes of violence and violent crime. Indeed, expert opinion has deemed that the evidence is sufficiently robust that new research should move beyond epidemiology and focus on treatment.[2,3]

However, uncertainties remain regarding the reported link. First, there are wide variations in risk estimates. These range from 7-fold increases in violent offenses in schizophrenia compared with general population controls[4,5] to no association in 1 prospective investigation.[6] Second, there is considerable uncertainty whether schizophrenia without substance abuse comorbidity is actually associated with violence. Large prospective and case-control studies have found no or only a weak association,[5,6] while other investigations from Finland, Denmark, and the United States report 3- to 4-fold risk increases.[7-9] Third, the possible contribution of genetic and early environmental factors in mediating the link between schizophrenia and violence has not been reliably studied.[10]

Conceptual models of violence in schizophrenia postulate that patients with schizophrenia are violent as a consequence of the psychopathologic symptoms of the disorder itself (eg, delusions, hallucinations[11]) or secondary to

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comorbid substance use (an established risk factor for violence[12]). An alternative model is that schizophrenia and violent behavior co-occur because of familial factors (genetic or early environmental) that are related to both (eg, personality traits such as irritability, poor anger management, or inadequate coping with stress).

If, as we hypothesize, the association of schizophrenia and violence disappears when substance abuse is accounted for and appropriate adjustments are made for confounding, this would suggest that assessment and treatment for substance abuse comorbidity should be prioritized in individuals deemed at risk. It would also explain why attempts to find psychotic symptoms associated with violence have produced contradictory results.[11,13,14] Therefore, by using longitudinal designs, we examined the relationship of schizophrenia with violent crime in Sweden from 1973 until 2006.

METHODS

Study Setting

We linked several nationwide population-based registries in Sweden: the Hospital Discharge Registry (HDR; held at the National Board of Health and Welfare), the Crime Register (National Council for Crime Prevention), the National Censuses from 1970 and 1990 (Statistics Sweden), and the Multi-Generation Register (MGR; Statistics Sweden). We also merged data with the causes of death register and the total population register (for emigration data) to provide information on loss to follow-up. In Sweden, all residents including immigrants have a unique 10-digit personal identification number that is used in all national registers, thus making the linking of data in these registers possible.

Probands With Schizophrenia and Controls

Using the HDR, which includes all individuals admitted to any psychiatric or general medical hospital for assessment and/or treatment (including forensic psychiatric hospitals and the few private providers of inpatient health care), we identified as cases individuals who fulfilled 2 criteria. First, they had been discharged from hospitals beginning in January 1, 1973, and had discharge diagnoses of schizophrenia on at least 2 separate inpatient hospitalizations according to the *International Classification of Diseases, Eighth Revision* (*ICD-8*) (1973-1986; diagnostic code 295), *International Classification of Diseases, Ninth Revision* (*ICD-9*) (1987-1996; code 295), or *International Classification of Diseases, 10th Revision* (ICD-10) (from 1997 onward; code F20), irrespective of any comorbidity. Second, they were born between 1958 and 1989, so that they were aged at least 15 years (the age of criminal responsibility) at the start of the study in 1973. We decided that schizophrenia had to be diagnosed on 2 separate occasions to increase diagnostic precision by minimizing false-positive diagnoses[15]; hence, those with only 1 diagnosis were excluded. More than 90% of individuals with schizophrenia were admitted during a 10-year period in Sweden.[16] Beginning in 1973, the hospital discharge register had national coverage. No information was available on patients treated solely in outpatient facilities.

For all individuals, data were also extracted on admissions from 1973 onward with principal or comorbid diagnoses of alcohol abuse or dependence (*ICD-8*: code 303; *ICD-9*: codes 303, 305.1; *ICD-10*: code F10, except x.5) and drug abuse or dependence (*ICD-8*: 304; *ICD-9*: 304, 305.9; *ICD-10*: F11-F19, except x.5). This information was used as a marker for comorbid alcohol and/or drug abuse disorders.

Diagnostic Validity and Reliability

Swedish HDR schizophrenia diagnoses show good concordance rates ($\kappa > 0.70$) with diagnoses based on Opcrit record review (a 90-item checklist of signs and symptoms generating *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) and *ICD* diagnoses developed for use in both European and US samples[17]) and interview (generating a *DSM* [Fourth Edition] [*DSM-IV*] diagnosis of schizophrenia).[18] In another study, 86% of HDR schizophrenia diagnoses corresponded with *DSM-IV* diagnoses of schizophrenia made from file-based reviews by psychiatrists.[19] However, the specificity is fair at best.[18] Hence, some individuals with schizophrenia are diagnosed as having other mental disorders during any particular inpatient episode, which forms the basis of our decision to use 2 diagnoses to define cases. Only about 1% of hospital admissions have missing personal identification numbers.[20] Consequently, the register has been widely used in psychiatric epidemiological investigations.[20,21]

In relation to substance abuse diagnoses, prior validity studies have found fair agreement between substance abuse diagnoses in the HDR and more comprehensive inpatient assessments.[22] We conducted a new and substantially larger analysis, which focused on individuals with schizophrenia. We extracted all individuals with a diagnosis of schizophrenia in the HDR and who had an inpatient forensic psychiatric assessment using a national register of all such evaluations from 1988-2000 (n=1638). The latter acted as our gold standard because these cases involved comprehensive multidisciplinary evaluations over 4 weeks in inpatient settings, yielding standardized consensus diagnoses.[23,24] The assessment included detailed review of medical, educational, and social services records; psychological testing; repeated mental state examinations; and interviews with family members and other informants. We found a κ of 0.37 (SE, 0.23; $P < .001$, corresponding to 68% agreement) for HDR diagnoses of comorbid substance abuse in individuals with schizophrenia, indicating fair to moderate agreement.[25]

We investigated 2 overlapping samples of individuals with schizophrenia. The first was a national sample of those with 2 or more hospital diagnoses of schizophrenia (n=8003). The second, which was a subgroup of the first sample, was all individuals with 2 or more hospital diagnoses of schizophrenia who had unaffected full siblings (n=4674). We identified com-

parison groups who had never been hospitalized for schizophrenia during the study period. The first was a random selection of 10 general population individuals matched by birth year and sex for each individual with schizophrenia (n=80 025 general population controls and n=8003 patients with schizophrenia). The second comparison was unaffected full siblings compared with those with schizophrenia (n=7780 full sibling controls and n=4674 individuals with schizophrenia), unmatched by age or sex and identified using the MGR.[26] The MGR connects each person born in Sweden in 1933 or later and ever registered as living in Sweden after 1960 to their parents.[27] For immigrants, similar information exists for those who became citizens of Sweden before age 18 years together with one or both parents.

Outcome Measures

Data on all convictions for violent crime beginning in January 1, 1973, were retrieved for all individuals aged 15 years or older (the age of criminal responsibility in Sweden). In keeping with other work, violent crime was defined as homicide, assault, robbery, arson, any sexual offense (rape, sexual coercion, child molestation, indecent exposure, or sexual harassment), illegal threats, or intimidation[20] (hence, burglary and other property offenses, traffic offenses, and drug offenses were excluded). Attempted and aggravated forms of included offenses, where applicable according to the Swedish criminal code, were also included. We followed these 2 cohorts until December 31, 2004, and a second set of cohorts until December 31, 2006.

Conviction data were used because the criminal code in Sweden determines that individuals are convicted as guilty regardless of mental illness. Therefore, it includes also those who are found not guilty by reason of insanity (who would be acquitted in other jurisdictions), persons who received custodial or noncustodial sentences, and individuals transferred to forensic hospitals (eg, individuals who were psychiatrically assessed and found to have had psychosis at the time of the offense). Furthermore, conviction data included cases in which the prosecutor decided to caution or fine. In addition, because plea bargaining is not permitted in Sweden, conviction data accurately reflect the extent of officially resolved criminality. The crime register has excellent coverage; only 0.05% of crimes had incomplete personal identification numbers in 1988-2000.[20]

Sociodemographic Covariates

Data on civil status and income were gathered from the 1970 and 1990 national censuses. For income, if there were no 1990 census data, we used 1970 data and converted these to the 1990 monetary value. This was then divided into tertiles (low, medium, and high) for the purposes of further analysis. When data on individual income were missing, we used the household income (also divided into tertiles) of the family of origin for those aged 15 years or younger at the time of the 1990 or 1970 censuses. Single marital status was defined as being unmarried, divorced, or widowed. Immigrant status was defined as being born outside of Sweden or having at least 1 parent born outside of Sweden. No data on homelessness were available. In the main analyses, missing data were not replaced by imputation or other methods.

Statistical Analyses

We estimated the association between schizophrenia and violent offenses with conditional logistic regression, as per related work using matched and/or sibling controls,[15,28] using the clogit command in Stata software, version 10 (Stata Corp, College Station, Texas). The clogit command fits conditional (fixed-effects) logistic regression models to matched case-control groups. Only offenses occurring after the second inpatient diagnosis of schizophrenia were included in the analyses. We analyzed data per convicted individual, regardless of the number of individual counts of crime per conviction.

Ten controls from the general population were selected for each case. In the sibling control study, all unaffected siblings were compared with each individual with schizophrenia. Age and sex were matched or adjusted for in all analyses. In the general population study, controls were matched by birth year and sex. In the sibling control investigation, age was adjusted for in analyses involving full-sibling comparisons by calculating the age difference (in years) between proband and sibling, and sex was also adjusted for.

We tested possible confounders (income, marital status, and immigrant status) by examining whether they were each independently associated with a diagnosis of schizophrenia and violent crime using χ^2 tests, and we included them as covariates in adjusted models if they were associated with violence in both univariate analyses at the .05 level of significance.[29] Immigrant status was a confounder only for risk of violent crime in those with schizophrenia compared with general population controls. Collinearity between confounders was tested using the collin command in Stata, and we found no evidence of significant collinearity—the mean variance inflation factor was 1.0 (where a value of 10 would indicate significant collinearity).[30]

Because substance abuse could be on the causal pathway between schizophrenia and violent crime, it has been argued that it is not appropriate to include it as a confounder in regression modeling.[31] Another argument for not including substance abuse as a confounder is whether effect modification occurred (whether the risk increase for substance abuse was of a similar degree in patients as it was in controls).

We used the likelihood ratio test (with a $P<.05$ indicating a significant interaction) and we also fitted an interaction term into the model to test this. In building the model, all significant confounders were included simultaneously in addition to the outcome of interest (violent crime). To test the validity of the model, we performed the Shapiro-Francia normality test on the residuals and found no evidence of nonnormality ($P=.50$).

Power calculations (with an α level of .10 and power of 90%) suggested that 750 cases and 7500 controls were needed to determine a 2-fold difference in rates of violent offenses and 2500 cases and 25 000 controls to determine a 1.5-fold difference.

Sensitivity Analyses

To corroborate our results, we performed a series of sensitivity analyses. First, to test whether there was any secular trend, we selected all individuals with 2 or more diagnoses of schizophrenia born between January 1, 1972, and December 31, 1981 (n=1348; ie, a subgroup of the first sample). We again randomly selected 10 general population controls matched by birth year and sex for each individual in this sample (n=13 480) and were able to follow up this cohort through December 31, 2006. Because there were only 633 cases with unaffected siblings in this cohort (and 829 unaffected siblings), we did not perform stratification on substance abuse for sibling comparisons. Second, we examined risk of severe violent offense in individuals with schizophrenia. For this analysis, we defined severe violence as homicide, serious (or aggravated) assault, rape, sexual coercion and child molestation, or robbery. Third, to investigate possible differential loss to follow-up for cases and controls, we examined risk of violent crime after excluding individuals who emigrated or died during follow-up. Fourth, we investigated the effect of the timing of substance abuse comorbidity on risk of violence in schizophrenia. Hence, we compared the risk of violent crime in those with a substance abuse diagnosis before or at the same time as their second schizophrenia diagnosis with general population controls, and the risk in those who had a substance abuse diagnosis after their second schizophrenia diagnosis in relation to general population controls. Fifth, because our analysis excluded individuals with missing data, we recalculated the risk estimates with the addition of these individuals. For this subanalysis, an extra category was assigned to missing income and marital status information so that the model included all cases and controls. Finally, we investigated whether diagnosis of schizophrenia based on 1 hospital diagnosis provided different risk estimates. For this analysis, we used the cohort described above who were born between 1972 and 1981 (n=2107 with schizophrenia and 21 070 randomly selected general population controls). This represented an additional 56% of individuals with schizophrenia compared with case ascertainment based on 2 hospital diagnoses.

The Regional Ethics Committee at the Karolinska Institutet, Stockholm, approved the study. Data were merged and anonymized by an independent government agency (Statistics Sweden), and the code linking the personal identification numbers to the new case numbers was destroyed immediately after merging. Therefore, informed consent was not required.

RESULTS

Basic sociodemographic information and substance abuse comorbidity among individuals with schizophrenia and controls in the 2 samples are presented in TABLE 1. The prevalence of convictions for violent crime in individuals with schizophrenia was approximately 12% to 13% (TABLE 2), with median times from discharge to offense of 1132 days for patients in the general population study and 1214 days for patients in the sibling comparison sample. Overall, 6583 patients and general population controls (7.5%) and 571 patients and their sibling controls (4.5%) died or emigrated during follow-up. In the general population study, there were 141 violent offenders (12.5%) among cases who died or emigrated during follow-up compared with 913 violent offenders (13.3%) among cases who did not die or emigrate during follow-up (χ^2_1=0.50; P=.48). Approximately 5% to 8% of control individuals were convicted of violent crimes ($P<.001$ for all comparisons; Table 2). There was an increased risk of violent crime among individuals diagnosed as having schizophrenia: adjusted odds ratios (ORs) were 2.0 (95% confidence interval [CI], 1.8-2.2) when general population controls were used and 1.6 (95% CI, 1.3-1.8)

Table 1. Sociodemographic Information and Substance Abuse Comorbidity Among Individuals With Schizophrenia vs Unaffected General Population Controls and vs Unaffected Full Siblings in Sweden

Variables	Individuals With Schizophrenia (n = 8003)	Unaffected General Population Controls (n = 80 025)	Individuals With Schizophrenia and Full Siblings (n = 4674)	Unaffected Full Siblings of Individuals With Schizophrenia (n = 8123)
Age at diagnosis, mean (SD), y	27.2 (6.4)	NA	26.6 (6.3)	NA
Age at first violent offense, mean (SD), y	25.3 (7.0)	24.4 (7.2)	30.4 (6.0)	22.8 (6.9)
Male, No. (%)	5243 (65.5)	52 427 (65.5)	3057 (65.4)	4132 (50.9)
Individual annual income, mean (SD), Sk [US $], in thousands[a]	50.3 (54.6) [6.6 (7.2)]	110.8 (70.3) [14.6 (9.3)]	52.4 (54.6) [6.9 (7.2)]	91.0 (65.9) [12.0 (8.7)]
Marital status of single, No. (%)[b]	6766 (94.9)	51 323 (76.8)	4125 (96.1)	5827 (82.6)
Substance abuse comorbidity, No. (%)[c]	1959 (24.5)	1863 (2.3)	1115 (23.9)	402 (4.9)

Abbreviation: NA, not applicable.
[a] In the comparison of individuals with schizophrenia vs unaffected general population controls, data on income were missing for 881 cases (11.0%) and 13 262 controls (16.6%); in the comparison of individuals with schizophrenia vs unaffected full siblings, data on income were missing for 379 cases (8.1%) and 1074 controls (13.2%).
[b] "Single" refers to being divorced, widowed, or never married. In the comparison of individuals with schizophrenia vs unaffected general population controls, data on marital status were missing for 875 cases (10.9%) and 13 221 controls (16.5%); in the comparison of individuals with schizophrenia vs unaffected full siblings, data on marital status were missing for 380 cases (8.1%) and 1069 controls (13.2%).
[c] Substance abuse comorbidity refers to the proportion with any inpatient admission for drug or alcohol abuse or dependence in 1973-2004.

when unaffected siblings were controls (Table 2).

We found evidence of effect modification between substance abuse comorbidity and schizophrenia on the risk of violent criminal convictions in the general population sample (likelihood ratio: $\chi^2_1 = 52.7$; $P < .001$; interaction term: $z = 10.1$; $P < .001$). Therefore, we stratified the analyses of the association between schizophrenia and violent crime by substance abuse comorbidity.

The rate of violent crime in individuals diagnosed as having schizophrenia and substance abuse comorbidity (27.6%) was significantly higher than in those without comorbidity (8.5%), which resulted in adjusted ORs of 4.4 (95% CI, 3.9-5.0) for violent crime in schizophrenia with substance abuse and 1.2 (95% CI, 1.1-1.4) in schizophrenia without substance abuse ($P < .001$ for interaction) (TABLE 3). For sibling comparisons, the rate of violent offense in individuals with schizophrenia and comorbidity was 28.3% compared with 17.9% among unaffected siblings and was 7.2% in schizophrenia without comorbidity compared with 5.4% in unaffected siblings. This corresponded to adjusted ORs for violent crime of 1.8 (95% CI, 1.4-2.4) in patients with substance abuse and 1.3 (95% CI, 1.0-1.4) in patients without substance abuse (likelihood ratio: $\chi^2_1 = 24.4$; $P < .001$; interaction term: $z = 4.9$; $P < .001$). The rate of substance abuse among unaffected siblings of cases with substance abuse comorbidity was 9.7% compared with 3.3% in siblings of cases without substance abuse comorbidity.

Risk of violent outcomes in schizophrenia was significantly increased compared with unaffected controls when a more severe definition of violent crime was used, when individuals who died or emigrated during follow-up were excluded, and when case ascertainment was based on only 1 hospital diagnosis of schizophrenia (TABLE 4). When we extended the follow-up period through 2006, risk estimates were significantly increased compared with general population controls and were nonsignificantly increased compared with unaffected siblings (Table 4). In addition, when follow-up was extended, we found a significant increase in the risk estimate for violent crime in cases with substance abuse comorbidity compared with general population controls. In patients with schizophrenia, 102 of 1012 (10.1%) without substance abuse comorbidity had at least 1 violent offense (adjusted OR, 1.8; 95% CI, 1.4-2.3) compared with 97 of 336 (28.9%) cases with substance abuse comorbidity (adjusted OR, 5.8; 95% CI, 4.4-7.6). When individuals with missing data on income and marital status were included into the model, risk estimates were also significantly increased compared with unaffected controls. For the general population comparison, the adjusted OR was 2.1 (95% CI, 1.9-2.1) and for the sibling control comparison, the adjusted OR was 1.5 (95% CI, 1.3-1.8).

The effect of the timing of substance abuse in schizophrenia was possible to analyze in the general population study, but not when using sibling control data for reasons of statistical power. Patients with schizophrenia diagnosed as having substance abuse on the same day or before their inpatient episode for schizophrenia had a lower rate of violent crime (15.6% or 112/716 [15.6%]) compared with those diagnosed as having substance abuse after their schizophrenia diagnosis (429/1243 [34.5%]). The corresponding adjusted OR for risk of violent offense compared with general population controls was 1.9 (95% CI, 1.5-2.5) in those with substance abuse before a diagno-

Table 2. Risk of Violent Crime in Individuals With Schizophrenia vs Unaffected General Population Controls and vs Unaffected Full Siblings

	Individuals With Violent Offenses, No. (%)			
Control Group	Individuals With Schizophrenia	Controls	Adjusted Odds Ratio (95% CI)[a]	Adjusted Odds Ratio (95% CI)[b]
Unaffected general population controls	1054 (13.2)	4276 (5.3)	2.8 (2.6-3.0)	2.0 (1.8-2.2)
Unaffected full sibling controls	571 (12.2)	617 (7.6)	1.6 (1.4-1.8)	1.6 (1.3-1.8)

Abbreviation: CI, confidence interval.
[a] The general population control group was matched by age and sex. The unaffected sibling control group was not matched but the comparison was adjusted for age and sex.
[b] The general population control group was matched by age and sex, and the comparison was adjusted by income (lowest vs middle and highest tertiles), marital status (single vs not single), and immigrant status (individual or at least 1 parent born outside Sweden). The unaffected sibling control group was not matched but the comparison was adjusted by age, sex, income, and marital status.

Table 3. Risk of Violent Crime in Individuals With Schizophrenia With and Without Substance Abuse Comorbidity vs Unaffected General Population Controls and vs Unaffected Full Siblings

	Individuals With Violent Crime Conviction, No. (%)				Adjusted Odds Ratio (95% CI)[a]	
Control Group	With Schizophrenia, Without Substance Abuse	Matched Unaffected Controls	With Schizophrenia and Substance Abuse	Matched Unaffected Controls	Schizophrenia Without Comorbid Substance Abuse	Schizophrenia With Comorbid Substance Abuse
Unaffected general population controls	513 (8.5)	3077 (5.1)	541 (27.6)	1199 (6.1)	1.2 (1.1-1.4)	4.4 (3.9-5.0)
Unaffected full sibling controls	256 (7.2)	312 (5.4)	315 (28.3)	321 (17.9)	1.3 (1.0-1.4)	1.8 (1.4-2.4)

Abbreviation: CI, confidence interval.
[a] The general population control group was matched by age and sex and the comparison was adjusted by income (lowest vs middle and highest tertiles), marital status (single vs not single), and immigrant status (individual or at least 1 parent born outside Sweden). The sibling control group was not matched but the comparisons were adjusted by age, sex, income, and marital status.

sis of schizophrenia. The adjusted OR was 6.4 (95% CI, 5.4-7.5) in those with substance abuse comorbidity after their diagnosis of schizophrenia. Adjustments were made for age, sex, marital status, immigrant status, and income.

Table 4. Risk of Violent Crime in Individuals With Schizophrenia in Sensitivity Analyses Using Different Follow-up Period, Outcome Measure, and Exclusion Criteria for Cases

Control Group	Individuals With Violent Crime Conviction, No. (%)		Adjusted Odds Ratio (95% CI)[a]
	Individuals With Schizophrenia	Controls	
1972-1981 birth cohort followed up through 2006			
Unaffected general population controls	199 (14.8)	668 (5.0)	2.8 (2.3-3.4)
Unaffected full sibling controls	40 (26.1)	46 (9.6)	1.5 (0.9-2.2)
Severe violent crime outcome[b]			
Unaffected general population controls	261 (3.3)	683 (0.9)	2.3 (1.9-2.7)
Unaffected full sibling controls	148 (3.2)	133 (1.6)	1.7 (1.3-2.3)
Excluding cases who died or emigrated			
Unaffected general population controls	913 (13.3)	3977 (5.3)	2.1 (1.9-2.3)
Unaffected full sibling controls	526 (12.3)	526 (7.5)	1.6 (1.4-2.0)
Only 1 hospital diagnosis of schizophrenia (in the birth cohort followed up through 2006)			
Unaffected general population controls	286 (12.7)	1002 (4.8)	2.5 (2.2-2.9)

Abbreviation: CI, confidence interval.
[a] The general population control group was matched by age and sex and the comparison was adjusted by income (lowest vs middle and highest tertiles), marital status (single vs not single), and immigrant status (individual or at least 1 parent born outside Sweden). The unaffected sibling control group was not matched but the comparisons were adjusted by age, sex, income, and marital status.
[b] Severe violent crime was defined as homicide, serious (or aggravated) assault, rape, sexual coercion and child molestation, and robbery.

COMMENT

We used complementary longitudinal study designs to investigate the risk of violence in individuals with schizophrenia compared with unaffected controls with varying degrees of relatedness to the index individual with schizophrenia. Apart from the large number of individuals diagnosed as having schizophrenia included in this report (n=8003), more than all previous longitudinal studies combined, this study advances knowledge in 2 other ways. First, to reduce misclassification by incorrect inclusion of nonpsychotic diagnostic groups such as personality disorder and substance abuse (which are themselves associated with violence[32,33]), we only included as cases those with schizophrenia diagnosed on at least 2 separate occasions. Second, we adjusted for confounding more precisely than prior work in a number of ways. We used unaffected siblings as controls, for the first time to our knowledge in this field. This design provides a powerful way to adjust for residual familial confounding. In addition, we accounted for cohort effects by adjusting for year of birth, previously found to be important in, for example, suicide research.[34]

Our study has 2 main findings. First, the association between schizophrenia and violent crime is minimal unless the patient is also diagnosed as having substance abuse comorbidity. Among patients without comorbidity, adjusted ORs from comparisons with unrelated general population controls or unaffected siblings were 1.2 to 1.3. It is possible that these risk increases would change if more sensitive measures than discharge diagnoses of substance abuse had been used. A recent study based on the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) also found no association between schizophrenia (with or without comorbid substance abuse) and any violence or serious violence, although this was based on 294 individuals with schizophrenia and may have been underpowered to detect any differences across groups. However, when all patients in the NESARC study were examined, substance abuse comorbidity did increase the risk of violence in those with mental disorder.[35] Although the NESARC sample included more than 18 times more individuals with depression than with schizophrenia, it suggests that similar mechanisms to that we found may mediate violent offense in other mental disorders. Expert opinion has suggested that schizophrenia increases the risk 4 to 6 times in men and possibly even more so in women.[1,31] However, these increased risks are not as relevant to individuals without comorbid substance abuse; hence, our findings suggest that assessment and management of violence risk should be prioritized in patients with schizophrenia and substance abuse comorbidity. Whether it is necessary to assess violence risk in all patients, as recommended in the current guidelines of the American Psychiatric Association with "substantial clinical confidence," the highest category of evidence, will depend on a variety of individual and local factors, including service provision.[36] On the other hand, our data concur with the importance of effective psychiatric treatment from a public health perspective[37] and the importance of evidence-based prevention strategies for dealing with substance abuse.[38]

The second main finding is the variation in violence risk depending on the degree of relatedness between the patient and the control group. Compared with unrelated general population controls, the risk of violent crime in individuals with schizophrenia and substance abuse comorbidity was increased 4-fold (OR, 4.4; 95% CI, 3.9-5.0). However, unaffected siblings had increased rates of substance abuse compared with unrelated general population controls, which meant that the risk increase for schizophrenia with substance abuse comorbidity compared with these siblings was substantially reduced (OR, 1.8; 95% CI, 1.4-2.4), suggesting familial confounding of this association. Familial confounding may occur through genetic susceptibility or early environmental effects.

This finding is consistent with 4 possible explanations for the increased risk of violence among patients with schizo-

phrenia compared with general population controls. First, it is possible that schizophrenia (with a predominantly genetic etiology) leads to substance abuse, which in turn increases the risk of violent criminality. Some limited support for this interpretation was found from the timing of substance misuse in relation to hospitalization for schizophrenia. We found that the risk of violent crime was higher when substance abuse was diagnosed after compared with before hospitalization for schizophrenia. However, considerable caution is warranted: the reliability of diagnoses of substance abuse in Swedish hospital registers is fair to moderate and information on timing is suboptimal since it requires inpatient treatment. Second, genetic susceptibility to substance abuse might lead to schizophrenia, which in turn increases the likelihood of violent behavior. A third possibility is a genetic susceptibility to schizophrenia in common with substance abuse and that both in turn are associated with violence. A final interpretation is a shared genetic susceptibility to substance abuse, schizophrenia, and violent criminality. Some support for the latter comes from longitudinal studies that have found that violence and serious aggression precede the diagnosis of schizophrenia,[39,40] even after controlling for preadolescent psychotic symptoms.[40] Although our data do not suggest one interpretation above the others, future work is necessary to establish the mechanisms responsible for the associations among substance abuse, schizophrenia, and violence. One promising approach would be to use molecular genetic studies, wherein a host of putative genetic markers exist.[41] Regardless of the nature of the mechanism, adequate substance abuse treatment for individuals with schizophrenia is likely to reduce the risk of violence and should be part of the routine assessment and management of all such patients. Within a sample of individuals with schizophrenia, a recent US prospective investigation has confirmed the importance of substance abuse in predicting violence in patients with schizophrenia and also found that childhood conduct problems are a strong predictor.[42] However, the risk of violence in schizophrenia with childhood conduct disorder compared with general population controls remains uncertain.

Study weaknesses include our reliance on hospital data for case ascertainment and comorbidity. Over a 30-year period, more than 90% of individuals in Sweden with schizophrenia will have been hospitalized at some point.[16] However, since we used 2 diagnoses of schizophrenia for inclusion, some individuals with schizophrenia would not have been included in our sample. Another weakness is that information on comorbidity was also based on hospital diagnoses, and it is likely that the effects of substance abuse have been underestimated. However, as the same approach was taken for cases and controls, this may not affect risk estimates if a similar degree of underestimation occurred. Although we relied on conviction data, other work has shown that the degree of underestimation of violence is similar in psychiatric patients and controls compared with self-report measures; hence, the risk estimates were not affected.[43] A further limitation is that we did not have data on whether treatment was received and the nature of such treatment. It is possible that treatment effects mediated some of the differences found herein. Recent work has shown that antipsychotic medication reduces the incidence of any violence over 6 months from 19% to 14%, although that investigation was underpowered to assess serious violence.[42] However, with median times to violent offense in the current study being around 3 years after hospital discharge, studies assessing the impact of treatment will need extended follow-up. Rates of violent crime and their resolution are similar across Western Europe, suggesting some generalizability to our findings.[44] Comparisons with the United States are more difficult due to differences in legal and judicial systems, but information on assault rates has been collected for 1981-1999. Police-recorded assault rates were 3.7 per 1000 population in the United States and 4.1 per 1000 in Sweden in 1981-1999.[45]

We conducted a number of sensitivity analyses to explore factors that could potentially influence the risk estimates. We found no changes to risk estimates when a more severe definition of violent crime was used or the criteria for case ascertainment for schizophrenia was 1 hospital discharge diagnosis rather than 2. Increasing the length of follow-up through 2006 provided further evidence of familial confounding in the association between schizophrenia and violent crime and the role of substance abuse comorbidity in increasing the risk. Further research is necessary to clarify temporal trends in violent offense in these patients, and alternative designs, such as interrupted time series analysis, should be considered.

One of the implications of these findings is in relation to stigma. The public perception of the dangerousness of psychiatric patients is pervasive and is a key factor in their stigmatization,[46] partly influenced by selective media coverage of high-profile cases.[47] As a consequence, some western governments have introduced specific laws for offenders who have mental disorders that focus on the assessment of dangerousness and public protection.[48] Moreover, the stigma of mental illness is considered to be the most significant obstacle to the development of mental health care.[49] Our findings on the mediating role of substance abuse and the marginally increased risk of violent offense in patients without substance abuse should contribute to a more informed debate about stigma in psychiatric patients.

In summary, we used longitudinal designs to investigate the risk of violent crime in patients with schizophrenia. Our study substantially increases the evidence base by including more individuals with schizophrenia than the previous studies combined and more precise methods to handle confounding. We demonstrate that the risk of violent crime in schizophrenia in patients without co-

morbid substance abuse is only slightly increased. In contrast, the risk is substantially increased among patients with comorbidity and suggests that current practice for violence risk assessment and management in schizophrenia may need review.

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Study concept and design: Fazel, Långström, Grann, Lichtenstein.
Acquisition of data: Fazel, Långström, Hjern, Lichtenstein.
Analysis and interpretation of data: Fazel, Långström, Hjern, Grann, Lichtenstein.
Drafting of the manuscript: Fazel, Lichtenstein.
Critical revision of the manuscript for important intellectual content: Fazel, Långström, Hjern, Grann, Lichtenstein.
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